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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE	Application Number	09/632,735
	Filing Date	August 4, 2000
	First Named Inventor	BAEZA-RAMIREZ
	Group Art Unit	1641
	Examiner Name	K. Padmanabhan
	Attorney Docket Number	2480-103

Title: **METHODS FOR DIAGNOSTIC AND/OR TREATMENT OF ANTIPHOSPHOLIPIDS ANTIBODIES-RELATED DISEASES AND DEVICES**

REQUEST FOR RECONSIDERATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the Office Action dated January 27, 2003 applicants request reconsideration of the above-identified U.S. patent application in view of the following remarks

REMARKS

In an Office Action dated January 27, 2003 claims 32, 35-38, 46, 48, 49, 52-59, and 91-95 all of the claims under consideration in the subject patent application, were rejected. Reconsideration of this application and allowance of the claims is respectfully requested in view the following remarks.

Claims 32, 35-38, 46, 48, 52-59, 91-92 and 94 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Loizou et al. (Clin. Exp. Immunol., 1985). Applicants submit that not all elements of the invention claimed are disclosed in the Loizou et al. reference. All the claims of the current application are directed to a method of assessing the amount of immune

damage in a patient suffering from an autoimmune disease based on the presence of anti-lipidic particle antibodies and correlating such with an illness associated with antiphospholipid antibodies as in independent claims 32 and 46. The Loizou et al. reference does not anticipate the claims of the present application as the reference merely discloses an ELISA for measuring IgG and IgM anti-cardiolipin antibodies. As has been established in Prof. Baeza's declaration attached as Exhibit I the antibodies disclosed in the Loizou et al. reference are very different from the antibodies in the present application. See paragraph 7 of the Baeza declaration. In particular, the invention is directed to anti-lipidic particles antibodies whereas Loizou et al. disclosed cardiolipin antibodies.

Furthermore, Applicants submit that in Loizou et al. (1985) there is not any mention at all about phospholipids associated in lipidic particles, which are special molecular arrangements obtained only in lipid bilayers such as liposomes containing some phospholipids such as cardiolipin, the formation of which exclusively occurs in the presence of inductors. See Baeza declaration at 6.

Thus, the antibodies in Loizou et al. are completely different from the anti-lipidic particle antibodies in the current invention. Therefore, determination of anti-cardiolipin by ELISA according to Loizou et al differs from what is claimed in the present application.

Withdrawal of the rejection is respectfully requested.

Claims 32, 35-38, 46, 52-59, and 91-95 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Stewart et al (US 5,840,587). Similarly, as in the rejection with respect to Loizou et al. not all elements of the claims are disclosed in Stewart et al. as independent claims 32 and 46 require a correlation between the measured anti-lipidic particle antibodies present in

the sample from the patient and the amount of immune damage in a patient suffering from an autoimmune disease. Stewart et al. limits the measurement to individual arrangements of specific lipids whereas the current claims require that the anti-lipidic particle antibodies interact with the lipidic particles that are being used for diagnosis, not with any phospholipid.

The Office Action states that Stewart discloses in one embodiment, cardiolipin, which is a hexagon II lipid particle, is used as the phospholipid of the method (Col. 8, lines 4-11). The reference also discloses the determination of antiphospholipid antibodies from serum of healthy individuals (Col. 10, lines 49-54).

In addition to the fact that cardiolipin may not be considered, in no way, as a hexagonal II lipid particle applicants submit that in Stewart et al. (1998) there is not any mention of phospholipids associated in hexagonal II phase which is a special tubular molecular arrangement of phospholipids obtained in an aqueous media only in the presence of divalent cations. Furthermore, in Stewart et al. (1998) there is not any mention of lipidic particles, which are special molecular arrangements obtained only in lipid bilayers such as liposomes containing some phospholipids such as cardiolipin, which formation occurs exclusively in the presence of inductors. Thus the anti-lipidic particle antibodies are very different from the antibodies as disclosed in Stewart et al. as is shown in the Baeza declaration, at 6. Therefore, determination of anti-phospholipid antibodies by using polystyrene microspheres treated with a particular phospholipid according to Stewart et al. dramatically differs from what is claimed in the present application.

Withdrawal of the rejection is respectfully requested.

Claims 32, 35-38, 46, 48-49, 53-55, 59 and 91-95 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ramirez et al. (1994 or 1997) in view of Sugi et al. (Blood, 1995). Applicants submit that the disclosure of Ramirez et al. does not teach or suggest that the antibodies obtained can be used for the diagnosis of an early phase of an autoimmune disease. The references merely teach the obtaining of the antibodies and that the antibodies can be used to study the presence of lipidic particles in different cellular types, allowing for a better understanding of the functional role of these structures. In addition, Sugi et al. teaches the use of an ELISA procedure for the detection of antiphospholipid antibodies. Furthermore, as is clear from the Baeza declaration the Ramirez et al. references do not teach or suggest a correlation between the detection of the antibodies and the first stages of an illness in a human. Baeza decl. at 8.

As described in Prof Baeza's declaration and in Figure F (attached as Exhibit II) the appearance of the anti-lipidic particle antibodies as well as the anti-cardiolipin, anti-nuclear, anti-DNA and lupus anticoagulant antibodies occurred in a time period which is particular for each animal or human being, as this depends on the immune response of each individual. In consequence it is difficult to limit the time period in which these antibodies appear. However, the formation of anti-lipidic particle antibodies always occurs before the formation of the anti-cardiolipin, anti-nuclear, anti-DNA and anti-coagulant antibodies. This experimental information is not taught, mentioned nor suggested by Ramirez et al. This references merely teaches the obtaining of the antibodies and that the antibodies can be used to study the presence of lipidic particles in different cellular types, allowing for a better understanding of the functional role of these structures.

In addition, according to the Baeza declaration a person of ordinary skill in the art could not have predicted the detection of the anti-lipidic particles antibodies to be associated with early stages of an illness in a human, at the time. Therefore, Ramirez el al. in view of Sugi et al. do not disclose nor suggest the diagnostic method of the invention allowing early diagnosis of autoimmune diseases as is claimed. Applicants respectfully submit that the claimed invention thus is not obvious over Ramirez et al. (1994 and 1997) in view of Sugi et al. Withdrawal of the rejection is respectfully requested.

Applicants submit that the assumption in the Office Action with respect to common ownership of the invention is correct. The subject matter of the claims in the present application was commonly owned at the time any inventions covered herein were made.

Applicants further note that as a response to previous arguments the Office Action states that the features upon which applicants rely (i.e., one step method of carrying out the invention) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

Applicants, in the previous response stated that the present application requires as one step in carrying out the invention the correlation of the presence of the amount of anti-lipidic particle antibodies. This limitation was included indeed as step (e) in claim 32, as amended. Applicants never made reference to a one step method.

Furthermore, the Office Action states that the claims recite a correlation as one of the first events in illness. Therefore, read broadly, the claim merely requires that there be some correlation between the antibodies and illness at some point after illness onset, which both the references clearly disclose. The limitation of "one of the first events" does not substantially

further limit the time period of illness correlation, as this terminology does not specify how early in the illness diagnosis must occur.

In a first instance, Applicants submit that neither Loizou nor Stewart teach nor suggest a correlation between anti-lipidic particle antibodies and illness. As discussed the references disclose antibodies very different from the antibodies in the present invention. Baeza at 7. Therefore neither reference can disclose the recognition with respect to a correlation with the first events of an illness in a human.

In addition, present claim 32 clearly limits the time period for which to correlate the presence of the antibodies of the present invention with illness. The early diagnosis may occur at any time between the detection of the anti-lipidic particle antibodies prior to the formation of anti-cardiolipin antibodies, lupus anti-coagulant, anti-DNA antibodies or anti-nuclear antibodies.

Also, the Office Action notes that Applicant's arguments that the antibodies of the present invention differ from Stewart is not convincing, as it is noted that a reference is, in no way, limited only to its examples. Therefore, although the reference discloses specific particles, these are just preferred. Applicants submit that in Figures C and E of the Baeza declaration schematic representations of the antigens used in Stewart et al. and the present invention are shown in comparison. In the present invention, lipids associated in lipidic particles in the bilayers of liposomes or cells are used as antigens (Figure C). In Stewart et al. (1998), polystyrene beads coated with cardiolipin or other phospholipids (Figure E). In Figures C and E it is shown that both antigens are clearly different from each other, in consequence antibodies against lipids associated in lipidic particles in liposomes or in cells are clearly different from

antibodies against lipids bound to a solid polystyrene beads. Similarly, the Baeza declaration clearly points out the difference between these antigens and antibodies. Baeza at 5-7.

In addition, the Office Action notes that applicant states that the provision of lipids in their native states is advantageous, but has not stated in what manner. In Applicant's previous response Applicants referred to the fact that in Stewart et al. the phospholipids are bound directly to the solid phase of the microspheres, probably in a molecular arrangement different to that found in cell membranes. In this invention however liposomes bearing lipidic particles are used to detect antibodies, considering that liposomes are experimental models of cell membranes they have the advantage of presenting lipids in a more native molecular arrangement (bilayer and lipidic particles) rather than the phospholipid coated microspheres. Thus, applicants submit, anyone with ordinary skills in the art will consider that it is always preferable to use antigens in a more native molecular arrangements like the liposomes bearing lipidic particles than the artificial polystyrene beads coated with cardiolipin, due to the fact that native antigens revealed more appropriately the physiological and pathological conditions of the cells than artificial or non native antigens.

Furthermore, the Office Action also states that although the antibodies between the present application and the reference may indeed be different, the claims require only anti-lipid particle antibodies, which the microspheres coated with antiphospholipid antibodies of Stewart is sufficient to meet. Applicants further submit this assertion is not true, because the claims of the present specification require anti-lipidic particle antibodies and lipidic particles in the bilayers of liposomes or cells as antigens. By no means are the microspheres coated with antiphospholipid antibodies, as recited by the Office Action, sufficient to meet this requirement. In addition, the

microspheres are coated with cardiolipin (Baeza declaration Figure E) and these are used to identify anti-cardiolipin antibodies, instead of anti-lipidic particle antibodies as the present invention does.

Finally, the Office Action notes in response to applicant's argument that Ramirez et al. does not teach the diagnosis of an early phase of autoimmune disease, it is noted that this recitation leaves open at exactly what point in the disease state the correlation must be shown. The reference clearly teaches the determination of antibodies in patients with antiphospholipid syndrome and SLE with the lipid particles being present in the cell membranes of the patients.

Applicants submit, that as described above and in Figure F, the Ramirez et al. references do not teach, mention or suggest the use of the anti-lipidic particle antibodies in the early detection of illness in a human. The appearance of the anti-lipidic particle antibodies as well as the anti-cardiolipin, anti-nuclear, anti-DNA and lupus anticoagulant antibodies occurs in a time period which is particular for each animal or human being, as this depends on the immune response of each individual. In consequence it is difficult to limit the time period in which these antibodies appear. However, the formation of anti-lipidic particle antibodies always occurs before the formation of the anti-cardiolipin, anti-nuclear, anti-DNA and anti-coagulant antibodies. This experimental information is not taught, mentioned nor suggested by Ramirez et al. This references merely teaches the obtaining of the antibodies and that the antibodies can be used to study the presence of lipidic particles in different cellular types, allowing for a better understanding of the functional role of these structures.

Applicants submit that the present application is now in condition for allowance.

Reconsideration and favorable action are earnestly requested.

RESPECTFULLY SUBMITTED,					
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